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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,648	12/19/2001	Heather J. Belmont	49663 (71758)	2636

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 03/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,648	BELMONT ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-7,30,31,38,39,41-45,47,112 and 113* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7,30,31,38,39,41-45,47,112 and 113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/19/05 has been entered. Applicant's amendment and response, originally filed on 11/3/05, has also been entered as requested. Claims 3, 8-29, 32-37, 40, 46, and 48-111 are canceled. Claims 1-2, 4-7, 30-31, 38-39, 41-45, 47, and 112-113 are pending and currently under examination. An action on the merits follows.

It is again noted for the record that although claims 1-2, 4-7, 30-31, 38-39, 41-45, 47, and 112-113 still read broadly on any non-human transgenic animal, the claims have been and continue to be examined in view of the elected subject matter, i.e. a transgenic mouse.

The amendment to the claims filed on 11/3/05 is objected to under 37 CFR 1.121(c). The amendment provides a listing of the current status of the claims which does not comply with the requirements of 37 CFR 1.121(c). Claims 42-45 are listed as "previously presented"; however, the claim language differs from the previous listing of these claims filed on 12/16/04. Further, the applicant's response indicates that these claims have been amended to delete reference to claim 40. Thus, these claims should have been identified as "currently amended" and contain

markings clearly indicating that these claims are amended, see 37 CFR 1.121(c)(2). Furthermore, claim 41 is listed as "currently amended", and contains markings for the addition of language in lines 11 and 13. However, the amendments were made in the previous version of the claim, see the amendment filed on 12/16/04. Thus, this claim should have been listed as "previously presented". **While the amendment has been considered on the merits, please note that future claim amendments and claim listings must comply with all the requirements of 37 CFR 1.121(c) in order to be considered fully responsive.**

Claim Objections.

The objection to claims 42-47 under 37 CFR 1.75(c) as being in improper form because the claims depend in the alternative on canceled claim 40, is withdrawn in view of applicant's amendments to the claims 42-45, and 47 to remove reference to claim 40.

The objections to claim 46 is withdrawn in view of the cancellation claim 46.

Claim Rejections - 35 USC § 103

The rejection of claim 112 under 35 U.S.C. 103(a) as being unpatentable over 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, and McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, is maintained.

The applicant's response does not address this rejection. As the applicant has not amended claim 112 or provided any arguments traversing the grounds of rejection over claim 112, the rejection of record stands.

As noted in the final office action, mailed on 6/3/05, Claim 112 was never amended to contain the limitation that the human T cell receptor loci are unrearranged and that the transgenic non-human mammal comprises human alpha and beta chains as was claim 1. Claim 112 continues to read broadly on a transgenic non-human mammal with inactivated endogenous TCR loci comprising a transgene comprising a plurality of human TCR V genes, D genes and/or J and C genes from any TCR loci. As such, the rejection of record stands over claim 112 for reasons of record.

The rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 under 35 U.S.C. 103(a) as being unpatentable over 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, Rowen et al. (1996) Science, Vol. 272, 1755-1762, and Rack et al. (1997) Blood, Vol. 90(3), 1233-1240, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant first presents arguments against each of the references individually. While these arguments have been addressed in turn, please note that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,*

800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the rejection is based on the combined teachings of Littman et al. in view of Mombaerts et al., McMurry et al., Rowen et la., and Rack et al.

The applicant argues first that the claims have been amended to recite that human T-cell receptor loci regulatory sequences control the human TCR expression and that Littman et al. teaches away from this limitation because Littman teaches that previous attempts by other to use heterologous T cell specific enhancers and promoters resulted in inappropriate expression of CD4, citing column 32, lines 15-22 of Littman. In response, applicant's amendment did not introduce the limitation regarding the species of regulatory sequences into all the pending claims. Only claim 1 has been amended to recite such a limitation. Thus, applicant's arguments regarding the use of human T cell regulatory sequences with human TCR transgenes only applies to claim 1 and claims depending on claim 1, i.e. 2, 4-7, and 30-31. Independent claims 38 and 41 do not include the limitation that the regulatory sequences are human. Thus, applicant's arguments regarding Littman et al. do not apply to claims 38-39, 41-45, 47, and 112-113. Further, the Office disagrees with the applicant's interpretation of the teachings of Littman et al. In column 28, lines 46-52, Littman et al. teaches, "A transgene encoding a heterologous lymphocyte transduction protein comprises structural sequences encoding a heterologous lymphocyte transduction protein, and generally also comprises linked regulatory elements that drive expression of the heterologous lymphocyte transduction protein in the nonhuman host." Littman et al. further teaches in column 28, lines 60-62, "When a heterologous transgene relies on its own regulatory elements, suitable transcription elements and polyadenylation sequence(s) are included"; and in column 28, lines 65-66 " Usually the promoter form the naturally-occurring

heterologous gene is used" and column 29, lines 11-14 "Likewise, it is usually preferred that an enhancer is included in a heterologous transgene, typically an enhancer from the cognate lymphocyte transduction gene of the non-human host or, less preferably, the enhancer from the heterologous gene". Thus, Littman et al. does in fact teach the use of transgenes in which the regulatory elements, both the promoter and enhancer, are derived from the naturally occurring regulatory elements for that transgene. Further, the applicant is reminded that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also *Celeritas Technologies Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998).

Turning to example 2 of Littman et al., it is noted that Littman et al. does **not** teach that no expression of human CD4 was achieved by previous attempts to express human CD4 in mice using heterologous T cell specific promoters and enhancers. Rather, Littman et al. teaches that the expression achieved was not limited to CD4 cells, and was thus "inappropriate". However, it is noted that the claims as written do not include any limitations regarding expression patterns of human TCR alpha and beta chains. Further, case law states that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d

1130, 1132 (Fed. Cir. 1994). Therefore, for the reasons set for above, applicant's arguments regarding the teachings of Littman et al. are not persuasive.

The applicant further argues that since in their opinion Littman teaches that heterologous regulatory sequences will not work in mice, the skilled artisan would be dissuaded from using the nucleic acids taught by Rowen et al. and Rack et al. which include human regulatory sequences. As noted in the previous paragraphs, however, the applicant has misinterpreted the teachings of Littman. Littman, as noted above, does **not** teach that no expression of human CD4 was achieved by previous attempts to express human CD4 in mice using heterologous T cell specific promoters and enhancers. Rather, Littman et al. teaches that the expression achieved was not limited to CD4 cells, and was thus "inappropriate". Again, the claims as written do not include any limitations regarding expression patterns of human TCR alpha and beta chains. In addition, please note that Littman et al. does in fact provide an example demonstrating that the human CD4 promoter successfully drives the CD4 specific expression of a human CD4 transgene in transgenic mice lacking endogenous CD4 expression. Thus, it is not agreed that Littman does not provide sufficient guidance to make a transgenic mouse according to the claims as written.

The applicant further argues that Mombaerts is not an "enabling" reference because, in the opinion of the applicant, Mombaerts does not provide sufficient guidance to make and use the disclosed mouse strains, and further that there is not evidence that the mice described in Mombaerts were available to the public. In response, the Office finds Mombaerts et al. to be sufficiently enabling for the mouse strains described and used in the experiments reported by Mombaerts et al. Mombaerts et al. teaches 3 different strains of mice which have inactivating

deletions in the TCR alpha loci, TCR beta loci, or TCR delta loci (Mombaerts et al., page 275). Please note that Mombaerts et al. teaches that these 3 strains were developed previously and that the specific details of their construction can be found earlier publications by the authors of Mombaerts et al. or others in the field. Mombaerts et al. further provides the citations for the specific references which give detailed particulars as to how each of the mice strains was constructed. In addition, Mombaerts provides data using these strains of mice. Thus, Mombaerts et al. clearly provides sufficient guidance for mice having the disclosed characteristics. Finally, it is not required that the office provide evidence that these mice were "available to the public". The teachings of Mombaerts et al. was clearly available to the public, which is all that is needed to make and use the mice strains disclosed in this reference. Further, in regards to the availability of these mice from Jackson Laboratories, as taught by Mombaerts et al., the applicant has not provided any evidence that refutes the teachings of Mombaerts et al. that these mice strains were in fact commercially available as of 1994. Thus, the arguments regarding Mombaerts et al. are not found persuasive.

Regarding the teachings of McMurry, the applicant argues that the mice disclosed produce non-functional TCR because the V region genes had mutations, and that therefore, McMurry does not teach transgenic mice comprising an unrearranged TCR locus that could productively rearrange and produce expression of detectable amounts of transgenic TCR. In response, the previous office action stated that McMurry et al. further supplements Littman et al. by teaching transgenic mice carrying the human unrearranged TCR delta gene minilocus. McMurry et al. teaches that the human TCR delta gene minilocus comprises unrearranged human multiple V, D, J, and C gene segments (McMurry et al., page 4553-4554). McMurry et al. also

teaches that these mice are capable of functionally rearranging the human TCR delta gene locus. Further, in regards to this rearrangement, McMurry et al. demonstrates that it is dependent on the human enhancer present in this construct. Therefore, McMurry et al. provides evidence for productive V,D,J,C rearrangement of a human delta loci in mice dependent on the presence of a human enhancer. McMurry et al. was not relied upon for teaching functional expression of TCR protein. Littman et al. was cited for these teachings. Littman et al. clearly demonstrates the expression of a human lymphocyte transduction protein in mice. Based on the productive rearrangement of the human V,D, J, and C genes in the transgenic mice taught by McMurry et al., the skilled artisan would have had a reasonable expectation that an unrearranged human TCR loci present in the germline of a transgenic mouse would be capable of rearranging into an expressible transgene. It is further noted that the rejection of record relies on Rack and Rowen for vectors comprising unrearranged human TCR alpha and beta loci for use in the methods disclosed by Littman et al. for making transgenic mice capable of expressing human lymphocyte transduction genes. Thus, applicant's arguments concerning the teachings of McMurry are not found persuasive.

Finally, the applicant argues that Rack et al. is not enabled because the TCR delta locus is present in the TCR alpha loci and because Rack doesn't teach how many J segments are in the isolated locus. In response, nowhere in Rack et al. do the authors state or suggest that the fact that the TCR alpha loci includes the TCR delta loci would somehow prevent the TCR alpha loci from productively rearranging. On the contrary, Rack et al. clearly teaches that rearrangement of the TCR alpha loci deletes the delta loci contained within it. Thus, the applicant's concerns that the skilled artisan would somehow be dissuaded from using the germline TCR alpha loci because

of the presence of the delta loci is unfounded. In addition, the markings in Figure 1 do not indicate that only 1 of each of the gene segments is present in the YAC, the marking are there to point out the transcriptional orientation of the genes. The isolated YAC, according to Rack et al., contains the majority, 70% of the unrearranged TCR alpha loci, including most of the V region genes through the delta locus and including the J alpha region and the C alpha region. Finally, since applicant appears to be making an argument that the YAC isolated by Rack would not work, i.e. would be inoperative, it is noted that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, **inoperability of the prior art**, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

The final argument set forth by applicant is that neither Rowen nor Rack provides motivation for the use of the human TCR loci as transgenes to generate transgenic animals. In response, it is again pointed out that the rejection of record is based on the **combined** teachings of Littman et al., Mombaerts et al., McMurry et al., Rowen et al. and Rack et al. The description and motivation for making transgenic mice with TCR alpha and beta loci comes directly from the teachings of Littman et al., see columns 8-9. Thus, applicant's arguments concerning Rowen and Rack are not found persuasive.

Therefore, for the reasons set forth in detail above, the rejection of record stands.

Claim Rejections - 35 USC § 112

The rejection of claims 1-2, 4-7, and 30-31 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of applicant's amendments to the claims.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your

application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER